Claims

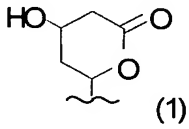
1. A method to enhance bone formation in a vertebrate subject which method comprises administering to a vertebrate subject in need of such enhancement an effective amount of any two of the following components

a) at least one nitric oxide (NO) generating system;

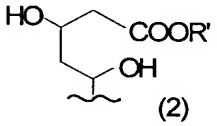
b) at least one statin-like compound; and

c) at least one phosphodiesterase (PDE) inhibitor.

2. The method of claim 1, wherein the statin-like compound is of the formula:



(1) or



(2)

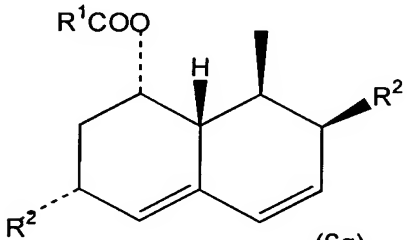
wherein each of formulas (1) and (2) is coupled through the indicated bond to an organic moiety of up to 40C.

3. The method of claim 2, wherein each of formulas (1) and (2) is coupled to –X-Y

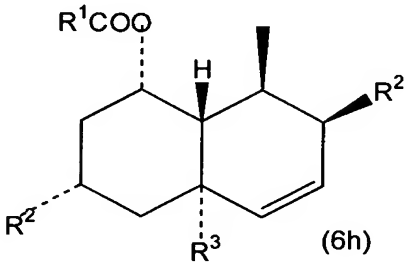
wherein X represents substituted or unsubstituted alkylene (1-6C), alkenylene (2-6C), or alkynylene (2-6C); and

Y comprises one or more carbocyclic and/or heterocyclic rings.

4. The method of claim 3, wherein Y is of the formula



(6g) or



(6h)

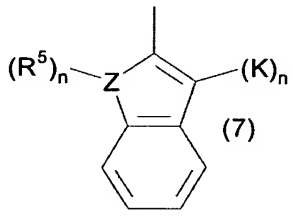
or a stereoisomer or mixture of stereoisomers thereof,

wherein R^1 is substituted or unsubstituted alkyl;

each R^2 is independently H, hydroxy, alkoxy (1-6C) or lower alkyl (1-4C);

R^3 is H, hydroxy, or alkoxy (1-6C); or

Y is of the formula



(7)

(8)

wherein each n is 1,

Z is N,

K comprises a substituted or unsubstituted aromatic carbocyclic or heterocyclic ring system which may optionally be spaced from the linkage position shown in formula (7) by a linker of 1-2C, or in formula (7), Z may be spaced from the carbon bonded to X by $=CR^6-$ wherein R^6 is H or linear, branded or cyclic alkyl (1-6C),

R^5 is H or linear, branched or cyclic alkyl, and

R' represents a cation, H or a substituted or unsubstituted alkyl group of 1-6C.

5. The method of claim 3 wherein X is selected from the group consisting of CH_2, $-CH_2CH_2-$; -CH=CH-; and -C≡C-.

6. The method of claim 5 wherein Y is of the formula (6g) or a stereoisomer or mixture of stereoisomers thereof.

7. The method of claim 6 wherein R^1 alkyl 4-5C.

8. The method of claim 6 wherein each R^2 is independently H, methyl or hydroxy.

9. The method of claim 5 wherein Y is of formula (7) as shown.

10. The method of claim 9 wherein Z is spaced from the carbon bonded to X by $=CR^6-$, wherein R^6 is H or linear, branched or cyclic alkyl (1-6C).

11. The method of claim 9 wherein K is a substituted or unsubstituted carbocyclic aromatic system.

12. The method of claim 11 wherein K is p-fluorophenyl.

13. The method of claim 4 wherein Y is of formula (8).

14. The method of claim 13 wherein K is substituted pyrrole.

15. The method of claim 14 wherein said substitutions comprise substituted or unsubstituted aromatic systems.

16. The method of claim 15 wherein the substitutions comprise alkyl (1-6C) and alkoxy (1-6C).

17. The method of claim 1 wherein said statin-like compound is atorvastatin, cerivastatin, lovastatin, mevastatin, simvastatin, fluvastatin, pravastatin, rosuvastatin or NK-104 in hydrolyzed or unhydrolyzed form.

18. The method of claim 1 wherein the statin-like compound is apamine or zaragozic acid.

19. The method of claim 1 wherein said nitric oxide generating system comprises an organic NO donor.

20. The method of claim 19 wherein said organic NO donor is glycerol trinitrate, isosorbide mononitrate, isosorbide dinitrate, erythrityl tetranitrate, pentaerythritol tetranitrate, or L-arginine.

21. The method of claim 20 wherein said organic NO donor is glycerol trinitrate or L-arginine.

22. The method of claim 1 wherein the nitric oxide-generating system comprises an NO synthesizing enzyme.

23. The method of claim 22 wherein the NO synthesizing enzyme is one or more isoforms of NO synthase and/or mitochondrial aldehyde dehydrogenase.

24. The method of claim 23 wherein said enzyme is provided as its encoding DNA.

25. The method of claim 24 wherein said encoding DNA is contained in a viral vector or in cells obtained from the subject or is naked DNA.

26. The method of claim 1 wherein said nitric oxide generating system comprises an agent that activates an NO-synthesizing enzyme or enhances the production thereof.

27. The method of claim 26 wherein said agent is cyclosporin A, FK506, felodipine, nicorandil, nifedipine, diltiazem, resveritrol, sapogrelate or quinapril.

28. The method of claim 1 wherein the PDE inhibitor is a nonspecific PDE inhibitor.

29. The method of claim 28 wherein said inhibitor is caffeine, theophylline, pentoxifylline, or 3-isobutyl-1-methylxanthine.

30. The method of claim 1 wherein the PDE inhibitor is specific for one or two phosphodiesterase families.

31. The method of claim 30 wherein said PDE inhibitor is dipyridamole, MY-5445, sildenafil, Zaprinast™, or rolipram.

32. The method of claim 1 wherein said two components comprise at least one nitric oxide generating system and at least one statin-like compound.

33. The method of claim 1 wherein the two components comprise at least one statin-like compound and at least one phosphodiesterase inhibitor.

34. The method of claim 1 wherein the two components comprise at least one nitric oxide generating system and at least one phosphodiesterase inhibitor.

35. The method of claim 1 wherein said two components are co-administered.

36. The method of claim 35 wherein said two components are co-administered in a single composition.

37. The method of claim 1 wherein said two components are administered sequentially.

38. The method of claim 1 wherein said subject is characterized by a condition selected from the group consisting of osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation.

39. The method of claim 1 which further comprises administering to said subject one or more additional agents that promote bone growth or that inhibit bone resorption.

40. A pharmaceutical composition in unit dosage form to enhance bone formation in a vertebrate animal which composition comprises a pharmaceutically acceptable excipient and an amount, effective to promote bone formation, of at least two of the following components

a) at least one nitric oxide generating system;

b) at least one statin-like compound; and

c) at least one phosphodiesterase inhibitor.

41. The composition of claim 40 wherein the statin-like compound is atorvastatin, cerivastatin, lovastatin, mevastatin, simvastatin, fluvastatin, pravastatin, rosuvastatin or NK-104 in hydrolyzed or unhydrolyzed form.

42. The composition of claim 40 wherein said nitric oxide generating system comprises an NO donor.

43. The composition of claim 42 wherein said NO donor is glycerol trinitrate or L-arginine.

44. The composition of claim 41 wherein the phosphodiesterase inhibitor is caffeine, pentoxifylline, theophylline, or 3-isobutyl-1-methylxanthine.

45. The composition of claim 40 which comprises at least one nitric oxide generating system and at least one statin-like compound.

46. The composition of claim 40 which comprises at least one nitric oxide generating system and at least one phosphodiesterase inhibitor.

47. The composition of claim 40 which comprises at least one statin-like compound and at least one phosphodiesterase inhibitor.